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PASSIVE SMOKING

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Assessment of the harmfulness to health of environmental tobacco smoke

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Report of the Health Council Committee on Passive Smoking

to

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The Minister and State Secretary for Welfare, Health and Cultural Affairs

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The Minister of Housing, Physical Planning and Environmental Protection
via the Minister for Welfare, Health and Cultural Affairs

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The Minister for Social Affairs and Employment
via the Minister for Welfare, Health and Cultural Affairs

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No. 1990/18, The Hague, 10 December 1990

FOREWORD

The present report was drawn up by the Health Council Committee on Passive Smoking. The members of the Committee are listed in Appendix B. With the presentation of the report to the Chairman of the Health Council the Committee considers its task completed.

The Hague, 10 December 1990

A.E.M. de Hollander
Secretary

Prof K.F. Kerrebijn
Chairman

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Dr Peter Hewitt Comments

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EXECUTIVE SUMMARY

1 Introduction

This report is issued by a Committee of the Health Council of the Netherlands at the request of the Dutch government.

In order to ascertain whether environmental tobacco smoke is harmful to health, the Committee has evaluated the most important articles published prior to June 1990. It has also consulted two important American reports (USS86, NRC86). The Committee outlines its report below.

2 . Evaluation of the results of epidemiological research

To evaluate the effect of exposure to environmental tobacco smoke one has to rely mainly on results of epidemiological research carried out among nonsmokers. This kind of research is beset by methodological problems which may distort the outcome. Distortion may be due to the following factors:

- the use of inaccurate measures of exposure and effect
- biased composition of the research groups to be compared (selection bias)
- bias of participants or researchers in reporting or compiling data (information bias)
- selective publication in scientific journals of results which indicate an effect (publication bias)
- the involvement of factors other than tobacco smoke (confounding factors).

The Committee examined the extent to which the published data might be distorted by any of the above factors. It used the

following criteria to assess whether exposure to tobacco smoke was a causal factor of the health effects found among nonsmokers:

- consistency of the results of various studies
- the magnitude of the increase in health risk as a consequence of tobacco smoke (the greater the increase, the greater the significance)
- the presence of a dose response relationship
- an appropriate time sequence of exposure and response (temporality)
- consistency with biological knowledge.

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3 Exposure of non-smokers to tobacco smoke

The tobacco smoke inhaled by a nonsmoker contains about 3,800 different substances. These include irritants, substances which can affect the nervous system, the respiratory tract, the immune system, blood and blood vessels and offspring, and also carcinogenic substances. The composition of directly inhaled smoke differs greatly from that of environmental tobacco smoke. Therefore the Committee considers it not possible to deduce from the health effects of active smoking to what extent exposure to environmental tobacco smoke causes effects in nonsmokers.

Exposure to tobacco smoke is widespread in the Netherlands. The Committee assumes that there are smokers in about six dwellings in every ten. In a survey carried out in 61 office buildings in the Netherlands, 41% of the nonsmokers questioned reported that tobacco was smoked in their immediate vicinity during working hours. Smoking considerably increases the indoor air concentrations of pollutants such as suspended particulate matter, nicotine, benzene, benzapyrene, nitrosamines and aldehydes.

In nonsmokers, traces of exposure to tobacco smoke are detectable in body fluids as certain substances, which include carcinogens and mutagens.

The Committee would point out that at present, occasional exposure to tobacco smoke is an inevitable concomitant

of people's social lives.

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4 Lung cancer

The Committee considers it likely that long-term exposure to tobacco smoke may increase the lung cancer risk of nonsmokers. This conclusion is based primarily on the results of a large number of surveys, in which the nonsmoking partners of smokers were found to have an increased lung cancer risk. By combining the various results, several authors have estimated that the increase in lung cancer risk might be between 10 and 60 percent. A number of studies have demonstrated a dose-response relationship.

The Committee considers an increase of the lung cancer risk to be biologically plausible since tobacco smoke contains substances which are carcinogenic in man and since the presence of tobacco smoke constituents or their metabolites has been demonstrated in the bodies of nonsmokers.

The Committee would emphazise that the apparent increase in the lung cancer risk could be partly due to flaws in the design of the epidemiological studies. As it is not known to what extent the results of the several studies are distorted, the Committee is of the opinion that quantitative estimation of the additional lung cancer risk of nonsmokers exposed to tobacco smoke is not possible at present.

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5 Other forms of cancer

On the basis of the epidemiological data currently available, the Committee cannot give an opinion as to whether exposure to tobacco smoke plays a part in the onset of cancer other than lung cancer in nonsmokers.

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6 Cardiovascular disease

The Committee does not expect short-term exposure to tobacco smoke to affect the circulation of healthy nonsmokers in normal circumstances. Nonsmokers with angina pectoris may occasionally experience symptoms in places with very high concentrations of tobacco smoke.

The Committee believes that the currently available data preclude a firm conclusion as to whether exposure to tobacco smoke is a contributary factor in the onset of and mortality from cardiovascular disease in nonsmokers. Epidemiological research carried out among nonsmoking partners of smokers provides only weak indications. The results of the several studies may have been confounded by differences in lifestyle between nonsmokers with and without smoking partners. So far researchers have not been able to control these differences adequately.

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7 Effects on children

The Committee concludes that exposure to tobacco smoke at home may have an adverse effect on children's health. The children of smoking parents run an increased risk of respiratory and middle ear infections. They may suffer more severely and more frequently from asthma and other respiratory symptoms. Development of the respiratory tract during childhood may be disturbed to some extent. In view of the association between the occurrence of chronic obstructive lung disorders in later life and respiratory disorders during the early years, the Committee does not exclude the possibility of long-term effects arising in children as a result of exposure to tobacco smoke.

In the opinion of the Committee, there is no doubt that smoking during pregnancy is harmful to the unborn child. Children of smoking mothers weigh less and are shorter on average at birth. The perinatal mortality rate is also higher. Although harmful substances from environmental tobacco smoke can pass through the placenta, it is not yet clear whether this can adversely affect the unborn children of nonsmoking mothers who regularly inhale tobacco smoke during pregnancy.

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8 Effects on the respiratory tract in adults

The Committee concludes that people with a disposition to asthma may be particularly sensitive to environmental tobacco smoke. They will suffer respiratory symptoms more fre-

quently at short-term exposure.

There are weak indications that adult nonsmokers who have been exposed for long periods to the tobacco smoke of smoking partners or colleagues experience respiratory symptoms more often than nonsmokers who are not similarly exposed. In addition, exposure has sometimes been found to cause a slight lung function decrease. The Committee believes that these indications do not yet permit a firm conclusion as to whether long-term exposure affects the respiratory tract. The effects found in surveyed groups of nonsmokers are small. It is not possible to ascertain whether these are the result of environmental tobacco smoke or other factors which have affected the respiratory tract, such as infections, illness, occupational circumstances or air pollution.

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9 Irritation and nuisance

Both smokers and nonsmokers may be bothered by tobacco smoke. People visiting smoke-filled places are at first overcome by the smell. This may be followed by irritation of the eyes and the mucous membranes of the nose, mouth and throat. Smell is the most sensitive nuisance indicator. The degree of ventilation needed to prevent nonsmokers from being hampered is much greater than that needed to avoid body odour nuisance. The latter serves as the general criterion for ventilation requirements.

The Committee believes that nuisance as a result of the smell and the irritating effects of tobacco smoke must be regarded as harmful to health. The continuous discomfort and the necessity to avoid public places constitute a fundamental assault upon a person's well-being.

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10 Summary from the health point of view

According to the health definitions laid down by the Health Council and the World Health Organization, it is not only the onset, aggravation or continuation of clinical symptoms or the reduction of life expectancy that are regarded as harmful to health. The extent to which the effects of ex-

posure to substances impinge on a person's ability to function normally is equally important (Gez77). In the opinion of the Committee, this principle also applies to exposure to tobacco smoke.

Short-term exposure to tobacco smoke can give rise to odour nuisance, irritation of the eyes and the mucous membranes of the eyes, nose, mouth and throat. It can also aggravate asthmatic symptoms. The Committee believes that such effects must be regarded as harmful to health in the light of the above principles. In the case of children, it takes the view that the effects of long-term exposure can be unequivocally regarded as harmful to health. The Committee also observes that the possibility of long-term exposure to tobacco smoke increasing the risk of lung cancer in nonsmokers cannot be excluded.

1 INTRODUCTION

1.1 Commissioning letter

On 5 April 1989 the State Secretary for Welfare, Health and Cultural Affairs wrote to the Health Council requesting recommendations on the possible harmful effects of "passive smoking". In his letter the State Secretary points out that research is yielding increasing indications of a connection between exposure to indoor tobacco smoke and damage to health. He also notes that the Tobacco Act provides for measures to control smoking in public buildings.

On behalf of the Minister for Social Affairs and Employment, the Minister of Housing, Physical Planning and Environmental Protection and himself, the State Secretary asks:

(a) Whether such damage is demonstrated by the research currently available,

and if so:

(b) Whether it is possible to evaluate this health risk to non-smokers within the framework of health criteria for air quality.

The State Secretary's letter is appended to the present report as Appendix A.

1.2 The Committee on Passive Smoking

Some time before formal receipt of the State Secretary's letter the Chairman of the Health Council set up a committee (on 2 February 1989) to draw up the recommendations as requested. The membership of this Committee on Passive Smoking - hereinafter referred to as "the Committee" - was as follows.

Chairman
Prof. K.F. Kerrebijn, Pediatrician

Other members
Dr R.P. Bos, Toxicologist
Dr B. Brunekreef, Environmental Epidemiologist
Dr E. Lebret, Environmental Epidemiologist
F.E. van Leeuwen, Epidemiologist
Prof. P.H. Quanjer, Internist & Physiologist
Dr G.M.H. Swaen, Epidemiologist

Advisers
A.P.M. Blom, Microbiologist
L. van Vliet, Adviser on Industrial Health

L. Wever, Lawyer

Secretary
A.E.M. de Hollander, Biologist

More information on the Committee is given in Appendix B.

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2 EVALUATION OF THE RESULTS OF EPIDEMIOLOGICAL RESEARCH

2.1 Introduction

The Committee was asked to pronounce on the possible harmful effects on health of exposure to environmental tobacco smoke (ETS) on the basis of research. The data available from laboratory tests on animals yield little useful information; it is uncertain, moreover, to what extent they can be applied to the exposure of humans. Applying data on the effects of active smoking to exposure to ETS is fraught with perils, in the Committee's opinion, since ETS differs considerably in its composition from directly inhaled smoke. The Committee considers this point in more detail in Chapter 3. To evaluate the effects of ETS on health we must rely mainly on the results of research on exposed humans.

For reasons of ethics and logistics it is impossible to test hypotheses on the effects on human health of long-term exposure to ETS empirically. Information has been obtained primarily from statistical analysis of results of research into the relationship between the occurrence of a particular effect and exposure to ETS "in the field". Research of this kind has a number of advantages: it is concerned with humans and with relevant exposure levels and circumstances. It also has its limitations, however, and to interpret the results of epidemiological research correctly we must acknowledge these. The Committee will therefore now discuss the often inevitable limitations inherent in the research and indicate how they can result in biased data.

2.2 Methods of epidemiological research

The methods of establishing the effects on health of exposure to ETS as used in epidemiological research are, in brief, as follows.

(a) Descriptive cross-sectional studies of population samples: the occurrence of particular disorders or symptoms in a sample at a particular moment in time is examined in relation to data on exposure to ETS.

(b) Prospective cohort studies: a sample is divided into groups on the basis of data on exposure to ETS. The study begins with the collection of these data and demographic and medical data. The researchers then ascertain whether differences develop over a period of time between the groups as regards the occurrence of disorders or symptoms.

(c) Retrospective studies of "occasional" cohorts on which data have been collected, in earlier postal surveys or in the course of other medical research, which were not originally intended to establish whether exposure to ETS has an effect on

health. The researchers try to trace as many as possible of the original sample to ascertain whether over the years a link has occurred between particular disorders and exposure to ETS.

(d) Case-control studies. These begin with the selection of a group of patients with a particular disorder. Their past exposure to ETS is compared with that of a control group of subjects not suffering from this disorder who are demographically as similar as possible to the patients.

(e) Intervention studies designed for other purposes, which can sometimes yield data suitable for measuring the effect on health of ETS. An intervention study is a type of prospective cohort study which in some respects comes close to empirical methods. The sample is divided into random groups. One or more groups are subjected to a particular intervention, e.g. a medical treatment or health programme; another group acts as reference group. The progress of the groups is followed to ascertain how much benefit the participants derive from the intervention.

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The results of epidemiological research are generally expressed as an estimate of the relative risk, i.e. the risk to exposed subjects of contracting a particular disorder divided by the same risk to non-exposed subjects. The certainty of the estimate is usually expressed as a 90% or 95% confidence interval (CI).

2.3 "Traps" in epidemiological research

Epidemiological research is not empirical. One of the consequent drawbacks is that factors which could contribute to an effect are often not completely controllable: thus the estimated contribution to effects of ETS may be either too high or too low. The Committee has made allowance for this and examined the literature critically. This section systematically discusses the "traps" which could result in an incorrect interpretation of the findings.

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2.3.1 Accuracy of exposure variables

Studies of the effects of ETS involve obtaining data on long-term exposure, as a rule by means of questionnaires. In the ideal case the exposure dose would be expressed as the number of cigarettes smoked in the environment (e.g. household or workplace) during a particular period. In most cases, however, the answer to the question "Do you have a partner who smokes?" has to suffice. Such rough indications give no information on exposure in other environments or on factors which influence exposure at home or at the workplace, e.g. size, occupation and ventilation of rooms.

Any estimate of exposure should relate to the period which is biologically significant for the effect in question. In the case of cancer or cardiovascular disease it is cumulative exposure, preferably related to age and physical development, that determines the occurrence of the disease. It is not possible, as a rule, to describe exposure in this way. In cohort studies groups of exposed subjects are usually classified on the basis of a single assessment; changes in exposure before and after the assessment are disregarded.

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The criteria for exposure to ETS usually distinguish between "greater" and "lesser" exposure. The so-called "random errors" in these quantifications are probably considerable. Random errors in estimates of exposure usually cause the effect in question to be underrated. Random errors in the measurement of confounders (see 2.3.5) could also influence the estimate of the effect, which in practice could cause the connection between exposure and effect to be overrated.

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2.3.2 Accuracy of effect variables

Researchers have looked at a wide range of possible effects of ETS. In the case of cancer and mortality from cardiovascular disease they generally have to rely on computer records and death certificates, which have inherent inaccuracies, e.g. absence of data on disorders other than the primary cause of death and inadequate histological classification of tumours.

The effect on the respiratory tract has been ascertained from questionnaires on symptoms and measurements of pulmonary function. The random error in the measurements is probably less than the error made in assessing dose from questionnaires.

Random errors made in the measurement of effect variables make the estimation of the relationship between dose and effect more inaccurate and cause the relative risk to be underrated.

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2.3.3 Distortion of results due to selection of samples (selection bias)

If the selection of subjects for the various groups in a study is influenced by factors related to exposure to ETS (as in case-control studies) or related to the disorder in question (as in cohort studies) the results may be distorted. Such "selection bias" can cause the risk of exposure to be either underrated or overrated. In cohort studies allowance has to be made for the possibility of subjects assigned to the control group being more sensitive to the effects of ETS than subjects in the exposed group: this could be the case, for instance, with subjects suffering from respiratory disorders, who are less likely to choose a smoker as a partner than those without such complaints. This type of selection bias causes the risk of exposure to be underrated. Another type of selection bias results from the fact that subjects with sensitive respiratory tracts rarely take up smoking: consequently young smokers often appear to have healthier lungs and respiratory tracts than non-smokers.

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2.3.4 Distortion due to prejudiced perception or reporting (information bias)

Data used to establish exposure or effect variables may be inaccurate in some samples owing to prejudice on the part of the respondents or the researchers, and this can result in distortion of the results.

In case-control studies awareness of the connection between disease and exposure to ETS can consciously or unconsciously influence the information on exposure given by

the patient or his or her relatives. There is also a danger that the researcher may question patients about exposure more closely than control subjects. Not all respondents give reliable information on their smoking. There are indications that the proportion of smokers/ex-smokers incorrectly classified as non-smokers is higher among housemates of smokers than of non-smokers. This could result in an upward distortion of the risk of exposure to ETS when comparing these groups (Lee88).

In cohort studies the researcher's perception of disorders or symptoms may be consciously or unconsciously influenced by his or her awareness of the subject's exposure.

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2.3.5 Confounders (variables which result in confouding bias)

Besides exposure to ETS, a host of other known and unknown factors are capable of having influenced the onset of particular disorders, e.g. diet or exposure to toxic substances at work. If these factors are related in some way to exposure to ETS the relationship between ETS and the effect in question may be distorted. These factors are then referred to as "confounders". The distortion can be reduced by collecting data on the influence of known confounders and correcting the results accordingly. A number of studies have been made of variables related to exposure to ETS (Fri83, Koo88a, Sve87).

Active smoking is without doubt one of the most important confounders, since it is a major cause of the effect under consideration in the study of the effect of ETS.

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2.3.6 Distortion due to selective publication of results (publication bias)

Selective publication of results which indicate that exposure to ETS has an adverse effect could lead someone assessing published findings to overrate the true risk. Editors of scientific journals may be more inclined to accept manuscripts containing findings that suggest a connection between exposure and effect than manuscripts containing findings that suggest there is no such connection. These are usually weaker findings which are not statistically significant. Researchers themselves may also incline towards indications of adverse effects when assessing previously collected data.

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2.4 Criteria for the assessment of research findings

The Committee has had to judge the value of the connections - or absence of connections - found in the research between exposure to ETS and the occurrence of disorders, since the researchers' perception may be based, at least partly, on chance or flaws in the design of the study.

Allowance can often be made for the role played by chance by applying the correct statistical methods. It is customary in scientific circles to describe a connection found between the occurrence of a particular disorder and exposure to a factor as statistically significant if the likelihood of the perception being based entirely on chance is less than

five percent. The size of the population samples was not always large enough to establish real effects of ETS with sufficient certainty.

In assessing the results of epidemiological research the Committee has been guided not only by the magnitude of the relative risks found but also by the likelihood of a result being determined by chance. The Committee has also tried - whether or not the results indicate an effect of ETS - to ascertain how far the distorting factors mentioned above could have played a part.

Epidemiologists have developed a number of criteria by which to judge the causality of a link found between exposure to a factor and the occurrence of disorders: consistency, the strength of the link, temporality, the existence of a dose-response relationship and biological plausibility (Hil71, Kle82). Although there is not total unanimity as to their application in the scientific literature, the Committee considers it has been able, by critical application of these criteria, to reach an assessment of the studies discussed here.

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Consistency

The probability of a real causal connection increases if a link between exposure to ETS and an effect is found in different population samples in different circumstances. This is also the case if a link is also found with other, to some extent comparable, types of exposure, e.g. in smokers or people exposed in their work or in the open air to substances that can occur in ETS.

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Strength of link

The strength of the link, expressed as the relative risk (see 2.2), is a yardstick for the importance of the factor under consideration. The higher the relative risk found, the less likely it is that the link is determined entirely by distorting factors.

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Temporality

Exposure to ETS can only be regarded as a causal factor if, between the exposure and the occurrence of the effect, a period elapses which is reasonably consistent with the latency period. In cross-sectional and case-control studies in particular it is often difficult to establish whether the correct sequence of exposure and effect has occurred.

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Dose-response relationship

A connection found between dose and response generally supports the conclusion that there is a real exposure effect. Allowance must be made, however, for the possibility that as exposure increases there could also be an increase in the influence of distorting factors or confounders.

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Biological plausibility

The plausibility of a causal connection between exposure to a factor and the occurrence of a particular disorder also increases if the perception accords with our understanding of

biological mechanisms. The presence of carcinogens in ETS, for instance, adds to our expectation that exposure will result in an increased risk of the development of certain types of tumour. Results of epidemiological research not supported by biological research are regarded as "hypothesis-generating", and further research is then needed to establish whether the hypothesis is to be accepted or rejected.

3 EXPOSURE OF NON-SMOKERS TO TOBACCO SMOKE

3.1 Environmental tobacco smoke (ETS)

ETS consists for the most part of the smoke released by tobacco as it smoulders between puffs: we refer to this here as sidestream smoke (SS). Only a small proportion is accounted for by mainstream smoke (MS), which is exhaled by the smoker or released from puffs on a burning cigarette, cigar or pipe. SS and MS differ in composition as a result of the difference in combustion temperature, among other factors. Various secondary chemical and physical processes such as oxydation, vapourization, condensation, deposition and dilution cause the composition and distribution of particle size to change as the smoke "ages".

Some 3,800 components have been identified in tobacco smoke, and these may be found in the gas or particle phase (USS86, NRC86, Eat89, Ben89). Toxic properties have been identified in a large number of these components. ETS contains irritants (e.g. aldehydes), substances that affect the nervous system (e.g. nicotine), respiratory tract (nitrogen oxides), immune system (benzene) and blood (carbon monoxide), as well as mutagenic or teratogenic substances and substances regarded as carcinogenic in humans (nitrosamines and polycyclic aromatic hydrocarbons) (Wyn67, IAR86, NRC86, USS86, Löf88, Löf89, Cla89, Sor89).

Dust is a major component of ETS. Inert dust particles affect the respiratory tract and can also act as carriers of other components, which are thus able to penetrate more deeply into the tract.

Tobacco smoke also contains radioactive particles (NRC86, Rau85). There are indications that in subjects exposed to ETS the normal intake of radioactive particles is increased, primarily indirectly, as a result of radioactive decay products of radon which occur in the environment (e.g. in the ground or building materials) attaching themselves to respirable smoke particles (Ber83, NRC86, Axe88).

Given the quantitative and qualitative differences in the composition of MS, SS and ETS, data on the effects of "active" smoking cannot, in the Committee's opinion, be used as a guide to the effects of exposure to ETS on non-smokers.

3.2 Exposure to ETS

The Committee defines exposure to ETS as an event in which people come into contact with ETS. Thus smokers can also be exposed. The Committee includes in the "exposed" category unborn children of mothers who smoke or are exposed to ETS.

Exposure takes place in different environments, e.g. the

home, the workplace, public buildings and other public places, cars, trains and aeroplanes. The total exposure is determined by the time spent in different environments and the ETS levels found there.

The Committee distinguishes between incidental exposure, i.e. brief exposure for periods lasting from minutes to a few hours, and long-term exposure, i.e. repeated exposure for periods lasting from days or months to virtually a lifetime. Incidental exposure could result in such things as odour nuisance, irritation of mucous membranes and aggravation of symptoms of chronic non-specific lung disease (CNSLD). Long-term exposure may be a factor in the occurrence of respiratory infections, CNSLD, cardiovascular disease and cancer.

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3.3 Determining exposure to ETS

Data on exposure can be obtained by a number of methods (with differing degrees of refinement), applied separately or in combination. The methods are:

(a) questionnaires, diaries of smoking
(b) measurements of levels of ETS components in environments
(c) measurements of individual exposure using portable sampling or measuring equipment
(d) biological monitoring (of effects), i.e. measurements of ETS components or their metabolites in tissue or body fluids (urine, saliva, serum).

Questionnaires (or diaries) can be used to divide the sample into smokers, ex-smokers and non-smokers. It is also possible to make a rough subdivision by degree of exposure to ETS using data on housemates or colleagues who smoke.

It is impossible to measure all the components of ETS to quantify the exposure. As a rule only one or two indicators are measured, and these should be:

(a) specific to ETS as far as possible, so as to rule out influence from other sources of pollution
(b) able to be measured even at low levels of ETS
(c) present in the smoke from different types of tobacco
(d) representative of the medically important effect of ETS.

Various components were measured to gain some idea of the pollution of indoor air by ETS, principally dust, carbon monoxide, hydrocarbons, nicotine, nitrogen oxides and benz(a)pyrene. None of these substances satisfies all the above criteria for indicators. Most field studies used the level of dust particles in indoor air.

When personal exposure is measured the variations in exposure to ETS in different environments are also recorded.

Measurements of indicators in tissue or body fluids (biological monitoring) provide information on the intake of ETS components into the body. Nicotine and one of its products (cotinine) in saliva, blood or urine are most commonly used because they are specific to exposure to tobacco smoke and detectable even at relatively low exposure levels. The various studies clearly demonstrate a link between the level of

nicotine or cotinine in body fluids and exposure to ETS (Jar83, Mat84, Cou87, USS86, Hal89, Hen89, Gre89, Jar89).

Exposure to ETS increases the mutagenicity of urine, but this is also influenced by factors other than tobacco smoke and thus unsuitable as a quantitative yardstick for exposure. Measurements of compounds of ETS components and DNA or proteins in body cells are likely to offer a way of quantifying exposure to ETS and its genotoxic effects. The methods of doing this which have been developed to date are not sufficiently specific to tobacco smoke nor, furthermore, are they sufficiently sensitive to measure exposure.

The levels of ETS in the various environments vary considerably, and since people's lifestyles can also differ considerably, there is a wide range of exposure levels.

Retrospective and cross-sectional studies are capable of showing structural exposure to ETS only indirectly and with a limited degree of accuracy. Questionnaires are the main method used (Kul86, Cog89); incidental measurements of indicator levels or personal exposure are available only in exceptional cases. It is not yet possible to use biological monitoring to estimate past exposure.

In prospective studies it is possible, in theory, to measure indicators in the home or in body fluids of subjects at particular times (Hol89, Sve87), but here too exposure is usually established from questionnaires.

In empirical studies of acute effects it is possible to carry out measurements to establish dose-response relationships.

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3.4 Dutch data on exposure to ETS

To gain some idea of the extent of the effects on health in the Netherlands data are needed on the number of people exposed to ETS and the dose.

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3.4.1 Long-term exposure to ETS

Long-term exposure is determined to a large extent by where people spend their time. Research by the Socio-Cultural Planning Agency indicates that the Dutch spend an average of 70% of their time at home. During a normal working week a maximum of 20% of their time is spent at the workplace (Knu83). Thus the main sources of structural exposure to ETS are housemates and colleagues who smoke. Young children fall into a special category, since they spend almost all their time at home: their exposure to ETS is determined mainly by the smoking habits of the people who look after them.

One or more occupants of some 60% of Dutch homes are smokers (Leb85, Hou87, Jon86, Dij88, Dij89, Table 1). Two major studies show that smokers smoke about 10 cigarettes a day at home. Women smoke an average of two more cigarettes at home than men (Leb85, Hou87, Dij88).

A study by the Netherlands Cancer Institute examined the smoking habits and exposure to ETS of some 600 women aged 20 to 55 in 1987 and 1988. Sixty-four percent of the women in the study were found to be non-smokers or ex-smokers. A quarter of these 385 or so subjects were exposed to tobacco smoke from housemates on a daily basis. From questions on previous

smoking habits of housemates the researchers established that 65% of this category were exposed to ETS on a daily basis in 1965, as against 51% in 1975. Exposure was greater outside the home than inside the home in six percent of the women non-smokers and ex-smokers (Lee90).

Measurements in a large number of dwellings show that smoking of tobacco products is the main source of respirable dust in the home. In homes where there was no smoking the mean level of respirable dust (RSP) over a period of a week was approximately the same as in the open air (30μg/m3). Smoking caused a rise in RSP levels of 10-100μg/m3 (2-5μg/m3 per cigarette smoked). Peak levels of RSP, depending on the number of cigarettes and the time of smoking, were in the hundreds of μg/m3. The levels of compounds such as nitrogen monoxide, carbon monoxide [and] volatile hydrocarbons (including benzene) also increased where there was smoking in the home (Leb85).

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Table 1 Percentage of homes with one or more smokers

Town	% with smokers	Source
Ede (n=174) post-war homes	60	Leb85
Rotterdam (n=102) pre-war homes	66	Leb85
Ede (n=103) post-1976 homes	61	Leb85
NE Brabant (n=779) Jan.85		Hou87
homes with primary school children	69	
with smoking mother	46	
with smoking father	52	
0 smokers	31	
1 smoker	39	
2 smokers	30	

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In homes in Arnhem Brunekreef and Boleij found a relationship between the mean level of dust (total dust, TSP) and the number of smokers per dwelling (Bru82). In a study of pulmonary function in schoolchildren in the IJmond area Hoek et al. found a connection between RSP level and the number of smokers in the dwelling, both during periods of air pollution and at other times (Hoe89).

Data on exposure to ETS at the workplace are scarce. In one study some 6,000 Dutch office workers were asked about their smoking habits and those of people in their environment. Of the non-smokers questioned 41% reported that they had

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smokers in their immediate vicinity while working (Pre90).

Mean RSP levels of 40-50$\mu g/m3$ have been measured in Dutch offices - slightly higher than those found by Lebret in homes without smokers, but considerably lower than in homes with smokers (Bre84, Leb85, Bra86).

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3.4.2 Incidental exposure to ETS

Research into the way the Dutch spend their time gives some idea of the amount of time spent in environments where exposure can take place (Knu83). American research indicates that levels of indicators such as RSP, nicotine and CO in public places were generally high (USS86). If these data also apply to the Netherlands, we must conclude that incidental exposure to ETS is virtually unavoidable nowadays.

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3.5 Foreign data

The number of smokers in Europe and the United States is gradually falling (Pie89). Recent publications indicate that the proportion of homes where there is smoking is also on the decline, but it is still over 50% (Sch77, Cha89, Som88, Neu89, Wie87). In a survey of some 38,000 American non-smokers 63% reported exposure to ETS. In 33% of these cases the exposure lasted for 10 hours or more a week, and in half of these for 40 hours or more a week (Fri83).

A large number of measurements of various indicators in public and non-public buildings indicate that ETS makes a substantial contribution to the pollution of indoor air by dust, nicotine, benzene, toluene, benz(α)pyrene, acrolein, aldehydes, nitrosamines, pyrene and carbon monoxide (USS86, Ste87, Kir88). Spengler et al. found mean RSP levels in homes approx. 20$\mu g/m3$ higher per smoker than in homes without smokers (Spe81). Statistical analyses of the data showed that each cigarette smoked contributed an average of about 1$\mu g/m3$ to the RSP level. In homes with full air conditioning the amount contributed was over 2$\mu g/m3$. Measurements of individual exposure made using portable sampling equipment for RSP and some volatile organic compounds, combined with logbook data on time spent, confirm that exposure to ETS at home and at the workplace determines the exposure to these substances to a large extent (Spe85, Wes86, Wal85, Wal86b, Wal87).

Danish research in 44 apartments showed that smoking is the main source of dust in the home. Mean dust levels (total suspended particulate matter, TSP) of 91, 169 and 475$\mu g/m3$ were measured in apartments where there was no smoking, light smoking and heavy smoking respectively (Rev87).

Relatively few measurements have been made of levels at the workplace. Weber et al. measured dust levels in 44 workplaces. Smoking raised the dust level by an average of 133$\mu g/m3$ (Web80). American measurements, on the other hand, show only slightly increased levels of indoor air pollution components at the workplace as compared with those in the home (NRC86, Ste87).

A comparison between American and Dutch measurements permits the cautious conclusion that the smoking of cigarettes results in higher average levels of ETS pollution in Dutch homes than in American homes. This probably has something to

do with the volume, spatial arrangement and ventilation of the dwellings.

Various studies show that the level of cotinine in the urine or saliva of children increases the more they are exposed to ETS (Ry189, Hen89, Hol89).

Mattson et al. found increased levels of cotinine in the urine of passengers and staff of an airliner up to 72 hours after the flight, even in passengers who had sat in the non-smoking compartment (Mat89).

Measurements of levels of thiocyanate in foetal serum and levels of nicotine or cotinine in amniotic fluid suggest that the unborn child of a non-smoking mother who regularly inhales ETS, or of a mother who smokes, is indirectly exposed to components of tobacco smoke (And82, Bot82, Bur82, Smi82, Etz85, Luc85).

A number of studies show that the amount of nicotine and cotinine in the plasma or urine of non-smokers exposed to ETS is about one percent of that in smokers (NRC86). It cannot automatically be concluded from this that the effect of exposure on non-smokers is only one percent of that on active smokers: nicotine is only one of the components of MS and ETS. As already noted, the composition of MS can differ considerably from that of ETS.

MacLure et al. (Mac89) found compounds of haemoglobin and two aromatic amines, including a substance capable of causing bladder cancer, in the blood of non-smokers. The level of these adducts depended on the exposure to ETS, which was established from the level of cotinine in the blood, among other factors.

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3.6 <u>Tobacco smoke and mutagenicity</u>

Van Houdt et al. (Hou84) found that the mutagenicity (ability to attack genetic material in cells) of air samples measured using the Ames Test increased with the number of cigarettes smoked in the home.

Various studies show that exposure to ETS increases the mutagenicity of urine concentrate in the Ames Test (Bo 83, So 85).

In the Committee's opinion these results support the supposition that exposure to ETS increases the risk of cancer. Exposure to ETS causes reactive compounds to form in the body which can be responsible for damage to macromolecules including DNA.

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3.7 <u>Trends in tobacco use</u>

Data from the Health and Smoking Foundation and the Central Bureau of Statistics indicate that the percentage of adult males and females who smoke is falling by about one percent a year. Smoking among the under-15s has declined sharply since the late seventies but has recently remained stable, around the nine percent mark (SVR90).

Tobacco consumption has dropped only slightly since 1986. Despite the fall in the percentage of smokers, consumption is still considerably higher than in 1970 (CBS87). Some graphs and tables from the annual report of the Health and Smoking Foundation (SVR90) are given at the end of this

chapter by way of illustration.

It is likely, given that the percentage of young people starting to smoke has fallen, that the percentage of smokers will continue to fall in the years to come. Analysis of data from six Western countries indicates that the percentage of smokers in more highly educated sections of the population is falling much more rapidly than among the less educated (Pie89, NCH89).

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3.8 Conclusions

The composition of directly inhaled smoke differs considerably in both quality and quantity from that of ETS. It is not possible, therefore, in the Committee's opinion, to use data on the effects of active smoking as a guide to the extent of the effects of exposure to ETS in non-smokers.

Exposure to ETS occurs on a large scale in the Netherlands. The Committee assumes that there are one or more smokers in about 60% of Dutch households at present. Smoking results in a considerably increased level of particulate-phase and gas-phase pollution in indoor air. The mean level of these substances in homes where there is smoking is higher, as a rule, than in offices where there is smoking.

Biological monitoring shows that exposure to ETS results in an increased level of ETS components in body fluids, including mutagens and carcinogens.

The Committee would point out that, in the present circumstances, incidental exposure to ETS is unavoidable with normal participation in social intercourse.

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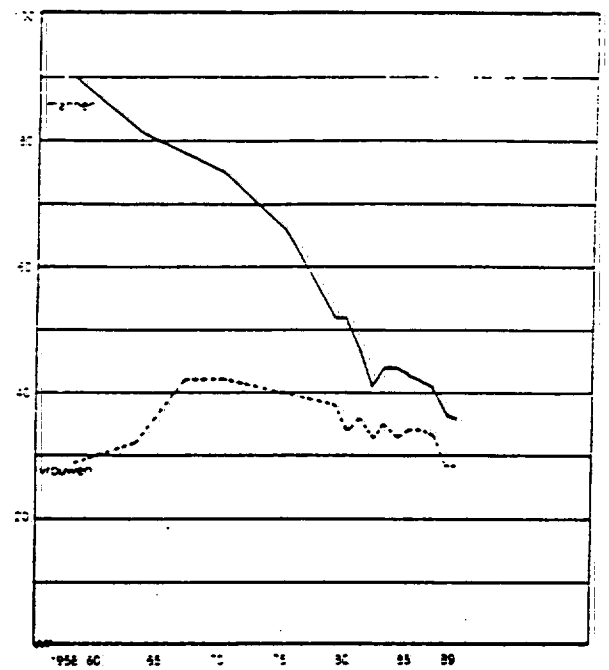
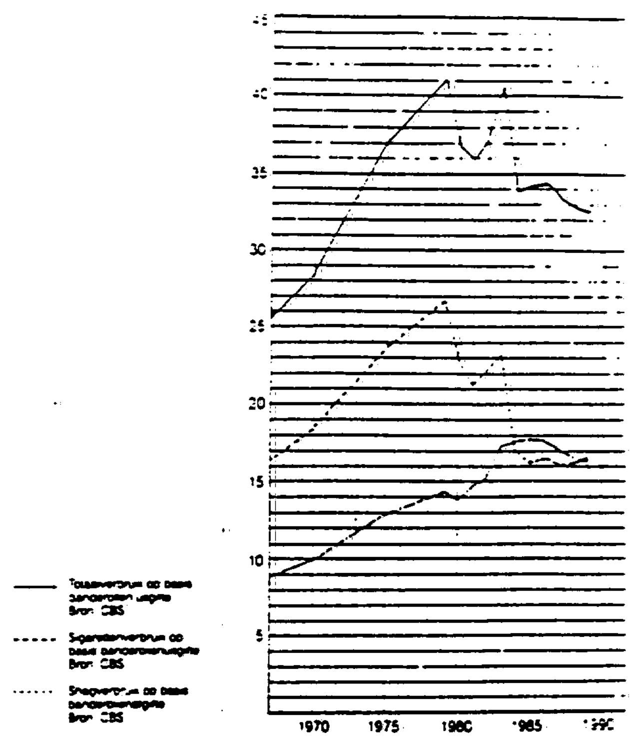
Aantallen rokers in percentages

1958-1989 in Nederland totaal 15 jaar en ouder



Sigaretten- en shagverbruik in Nederland in miljarden stuks.



Roken in Nederland (1958-1989):
Percentage rokers per leeftijdsgroep naar geslacht.

Leeftijd	15-19		20-34		35-49		50-64		65+		15-65+		Totaal
Geslacht	M	V	M	V	M	V	M	V	M	V	M	V	
Jaar	%	%	%	%	%	%	%	%	%	%	%	%	%
1958	-	-	91	46	91	32	89	3	88	5	90	29	50
1963	-	-	78	45	85	38	81	30	76	[illegible]	82	32	[illegible]
1967	58	57	79	58	90	46	82	26	55	13	78	42	[illegible]
1970	55	57	77	57	77	48	78	[illegible]	74	13	75	42	[illegible]
1975	46	48	58	58	65	47	68	29	56	12	66	42	52
1979	29	39	56	52	58	40	51	30	47	13	52	38	45
1980	30	31	56	44	54	38	56	28	52	11	52	34	43
1981	27	30	49	48	50	39	51	28	51	13	47	36	41
1982	18	27	45	45	44	36	45	27	43	13	41	33	37
1983	22	28	46	48	50	39	47	25	41	12	44	35	40
1984	17	24	48	44	48	36	49	29	43	13	44	33	39
1985	22	23	46	44	48	39	47	29	42	13	43	34	39
1986	22	22	46	45	46	37	45	29	41	12	42	34	38
1987	21	22	41	42	47	37	44	31	39	12	41	33	37
1988	19	19	39	38	41	34	39	25	35	11	37	29	33
1989	17	20	37	35	42	35	37	26	34	13	36	29	33

Bron: Gadourek, Riskante gewoonten (1958)
NOP, TCN Enquêtes, Stichting Volksgezondheid en Roken
NIPO-Enquêtes (1979-1989)

Roken in Nederland (1978 - 1988):
Percentage rokers per leeftijdsgroep naar geslacht: Jeugd

Jaar	1978		1979		1981		1982		1983		1984		1985		1986		1987		1988		1989	
Geslacht	M	V	M	V	M	V	M	V	M	V	M	V	M	V	M	V	M	V	M	V	M	V
Leeftijd	%	%	%	%	%	%	%**	%**	%	%	%	%	%	%	%	%	%	%	%	%	%	%
10-12 jaar	21	10	11	8	16	10	6	4	5	3	4	4	1	3	2	4	3	2	3	3	3	1
13-14 jaar	37	42	30	35	23	27	21	22	17	22	19	22	20	24	19	22	18	15	15	20	20	17
Totaal	28	28	24	21	20	19	10	12	10	12	10	12	[illegible]	13	5	11	9	9	8	10	10	8
10-14 jaar	27		22		19		12		**		**		13		10		9		9		9	

Bron: Stichting Volksgezondheid en Roken. Nipo-enquêtes naar rookgewoonten onder jeugd 1978-1989

* in 1980 is geen onderzoek verricht
** voor de leeftijdsgroep 10-14 was de vraagstelling tot 1982 "rook je wel eens of rook je helemaal niet?" vanaf 1982 is de vraagstelling "heb je in de afgelopen 4 weken gerookt?"

Gegevens over roken in Nederland (SVR90)

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Percentages of smokers
Total in the Netherlands aged 15 and over (1958-89)

males
females

Cigarette and cigarette tobacco consumption in the Netherlands (x 1,000 million)

Total consumption (based on revenue stamps issued)
Source: CBS
Cigarette consumption (based on revenue stamps issued)
Source: CBS
Cigarette tobacco consumption (based on revenue stamps issued)
Source: CBS

Smoking in the Netherlands (1958-89):
Percentage of smokers by age group and sex

Age [cijfers a.u.b. overnemen] Total
Sex M F [enz.]
Year

Source: Gaddurek, Riskante gewoonten [Dangerous habits] (1958)
NOP TON surveys, Health and Smoking Foundation
NIPO surveys (1979-89)

Smoking in the Netherlands (1978-88):
Percentage of smokers by age group and sex: young people

Year [cijfers a.u.b. overnemen]
Sex M F [enz.]
Age
10-12 yrs
13-14 yrs
Total
10-14 yrs
Source: Health and Smoking Foundation, Nipo surveys into smoking habits among young people, 1978-89
* No survey in 1980
** Before 1982 the question for the 10-14 age group was "Do you smoke sometimes or not at all?" From 1982 the question was "Did you smoke during the past 4 weeks?"

Data on smoking in the Netherlands (SVR90)

4 LUNG CANCER

4.1 Results of epidemiological research

Results of over twenty studies of the connection between exposure to ETS and the occurrence of lung cancer in non-smokers have been published since 1981. The comparison was usually between non-smoking partners of smokers and non-smoking partners of non-smokers. Some more recent studies also investigated smoking by colleagues and parents. Altogether these studies examined just under 1,500 cases of lung cancer in non-smokers, almost 90% of them women.

Table 4.1 shows the results of the most important studies in the form of the relative risks of lung cancer (see 2.2) in non-smokers exposed to ETS and the associated 95% confidence intervals (95% CI). For a detailed description of the studies the reader is referred to the accounts of the National Research Council (NRC86), the US Surgeon General (USS86), Saracci et al. (Sar89) and Spitzer et al. (Spi90).

As can be seen from Table 4.1, the results of most of the studies point to a slightly increased lung cancer risk in non-smokers as a result of long-term exposure to ETS due to smoking by housemates. The increase in the risk was statistically significant in only a few studies.

Some studies found a connection between dose and response where exposure was quantified on the basis of (a) estimated numbers of cigarettes smoked by partners or (b) duration of exposure. Other studies did not find a connection of this kind or did not look for one.

Repace and Lowrey compared the occurrence of lung cancer in Seventh-Day Adventists, who are presumed to live and work in a tobacco-smoke-free environment, with that in a demographically comparable group of non-smoking Americans. The latter's lung cancer risk was 2.4 times higher than that of the Seventh-Day Adventists. The authors supposed that part of the increased lung cancer risk was due to exposure to ETS (Rep86, Phi80).

Table 4.1 Results of the most important epidemiological studies of lung cancer in non-smoking partners of smokers

Source	Number of non-smokers with lung cancer	Sex	Relative risk	95% CI	Country
Prospective cohort					
Garfinkel 1981		F	[cijfers a.u.b.		USA
Hirayama 1984		F	overnemen:		Japan
Gillis 1984		F	komma wordt		Scotland
		M	punt!]		
Hole 1989*		F+M			Scotland
Case-control					
Chan 1982		F			Hong Kong
Correa 1983		F			USA
		M			
Trichopolous 1983		F			Greece
Buffler 1984		F			USA
		M			
Kabat 1984		F			USA
		M			
Garfinkel 1985		F			USA
Wu 1985		F			USA
Akiba 1986		F			Japan
		M			
Lee 1986		F			UK
		M			
Dalager 1986		F+M			USA
Pershagen 1986		F			Sweden
Humble 1987		F			USA
Lam 1987		F			Hong Kong
Gao 1987**		F			China
		F			
		F			
		F			
Koo 1988		F			Hong Kong
Janerich 1990***		F+M			USA

* Cohort partly the same as in Gilles et al. 1984
** Exposure for <20, 20-29, 30-39, >40 years resp.
*** Exposure expressed in smoker-years (number of smokers x number of years spent in household): 1-20, 25-49, 50-74, 75-99, ≥100 resp.

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Tabel 4.1 Resultaten van de belangrijkste epidemiologische onderzoeken naar longkanker bij niet-rokende partners van rokers.

bron	aantal niet-rokers met longkanker	sexe	relatief risico	95%-BI	land
prospectief cohort					
Garfinkel 1981	153	V	1,18	0,90- 1,54	USA
Hirayama 1984	183	V	1,63	1,25- 2,11	Japan
Gillis 1984	8	V	1,00	0,10- 4,91	Schotland
	6	M	3,25	0,60-17,65	
Hole 1989*	9	V+M	2,41	0,45-12,83	Schotland
patiënt-controle					
Chan 1982	84	V	0,75	0,45- 1,31	Hongkong
Correa 1983	22	V	2,03	0,81- 5,08	USA
	8	M	2,29	0,30-17,33	
Trichopoulos 1983	62	V	2,11	1,17- 3,78	Griekenland
Buffler 1984	41	V	0,80	0,32- 1,99	USA
	11	M	0,50	0,14- 1,83	
Kabat 1984	24	V	0,79	0,25- 2,48	USA
	12	M	1,00	0,20- 5,06	
Garfinkel 1985	134	V	1,23	0,81- 1,86	USA
Wu 1985	31	V	1,20	0,60- 2,50	USA
Akiba 1986	94	V	1,48	0,87- 2,52	Japan
	19	M	2,45	0,45-13,45	
Lee 1986	32	V	1,03	0,41- 2,58	UK
	15	M	1,30	0,37- 4,54	
Dalager 1986	48	V+M	1,47	0,76- 2,85	USA
Pershagen 1986	67	V	1,27	0,75- 2,18	Zweden
Humble 1987	20	V	2,16	0,84- 5,52	USA
Lam 1987	202	V	1,65	1,16- 2,35	Hongkong
Gao 1987**	57	V	1,0	-	China
	63	V	1,1	0,7 - 1,8	
	78	V	1,3	0,8 - 2,1	
	48	V	1,7	1,0 - 2,9	
Koo 1988	86	V	1,54	0,89- 2,67	Hongkong
Janerich 1990***	191	V+M	0,78	0,36- 1,67	USA
			0,80	0,43- 1,50	
			1,19	0,63- 2,27	
			1,80	0,83- 3,90	
			1,13	0,56- 2,28	

* deels hetzelfde cohort als bij Gilles et al 1984

** blootstelling respectievelijk gedurende <20, 20-29 jaar, 30-39 jaar, >40 jaar

*** blootstelling uitgedrukt in 'rokersjaren' (aantal rokers x aantal verblijfsjaren in huishouden), respectievelijk: 1-20, 25-49, 50-74, 75-99, ≥ 100

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4.2 Combined studies

In virtually all the studies the samples of non-smokers turned out to be too small to rule out the possibility of the effect of exposure to ETS found being based on pure chance. Various authors have therefore computed a combined relative lung cancer risk using data from various studies. In this way Wald et al. and Blot and Fraumeni and the authors of the NRC report did in fact establish a statistically significant increase in the lung cancer risk as a result of exposure to ETS (Wal86a, Blo86, NRC86).

The first-mentioned team analysed the results of three prospective cohort studies and ten case-control studies. They combined the separate relative risks, weighted for the size of the samples, and computed a combined relative lung cancer risk of 1.35 (95% CI: 1.19-1.54). The authors estimated that in the United States one in three cases of lung cancer in non-smoking partners of smokers and one in four in all non-smokers could be ascribed to exposure to ETS. The assessment of the risk of lung cancer given in the National Research Council report was based on their analysis.

Blot and Fraumeni combined data from ten case-control studies and two cohort studies. They computed a combined relative risk of lung cancer of 1.3 (95% CI: 1.1-1.5) for non-smoking partners of smokers. Combining the results of the studies which distinguished between partners who were light and heavy smokers they arrived at a relative risk of lung cancer of 1.7 (95% CI: 1.4-2.1) for non-smoking partners of heavy smokers.

Meijers and Swaen (Mei88) combined the results of 11 case-control studies and computed a combined relative lung cancer risk of 1.3 for exposed non-smokers. No confidence interval was calculated. On the basis of this estimate and certain suppositions concerning the percentage of exposed non-smokers and the percentage of deaths from cancer among non-smokers they calculated that exposure to ETS in the Netherlands must result in almost three additional deaths from lung cancer per million of population per year. The authors based these figures on CBS statistics for 1985 indicating total annual deaths from lung cancer of approx. 600 per million of population, including some 19 non-smokers. They concluded that the risk due to exposure to ETS exceeds the officially accepted risk due to exposure to carcinogens in the environment.

Fig. 4 is a compilation by the Committee of the published findings of case-control studies. The relative risks and confidence intervals have been computed in line with Wald et al. (Wal86a). Fig. 4 also shows the combined relative risk from all the findings.

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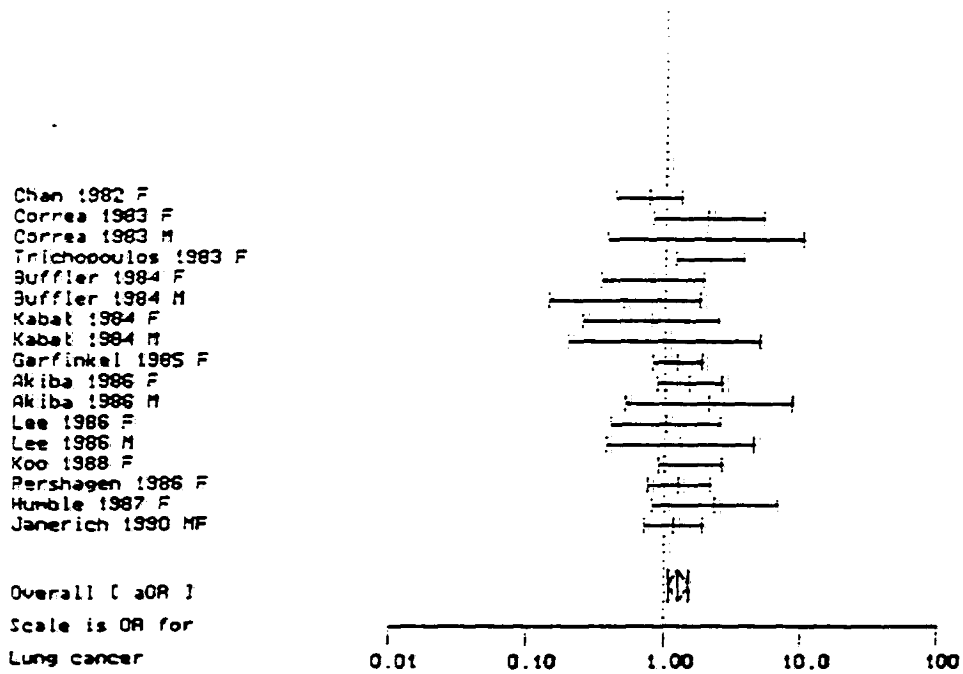
4.3 Possible distortion of findings

To what extent can the influence of long-term exposure to ETS on the lung cancer risk of non-smokers found in the research be explained in terms of flaws in the research

design? To answer this question the Committee will now discuss the principal distorting factors.



Figuur 4 Overzicht van de uitkomsten van patiënt-controle-onderzoek naar longkanker bij niet-rokende partners van rokers, uitgedrukt in het relatief longkankerrisico (puntschatting en 95%-betrouwbaarheidsinterval) van partners van rokers ten opzichte van partners van niet-rokers (F = resultaten voor vrouwen, M = resultaten voor mannen)

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[Figuur 4 a.u.b. overnemen]

Fig. 4 Findings of case-control studies of lung cancer in non-smoking partners of smokers, expressed as relative lung cancer risk (point estimation and 95% confidence interval) for partners of smokers compared with partners of non-smokers (F=females, M=males)

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4.3.1 Innaccuracy of exposure variables

The accuracy of the exposure variables used is limited. The main distinction is between greater and lesser exposure (see Chapter 2). The inability to establish the dose precisely causes the risk of lung cancer to be underrated, since the control group of non-smoking partners of non-smokers is also exposed to ETS to some extent, e.g. in public transport or at work. Wald et al. (Wal86a) and the NRC report (NRC86) correct for this by multiplying the relative risk found by a factor of 1.18 and 1.08 respectively.

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4.3.2 Accuracy of effect variables

The lung cancer diagnoses were not based on histopathological examination in every study. Secondary tumours seeded from primary tumours elsewhere unconnected with smoking could therefore have been taken to be primary lung tumours. As long as the misclassification is equally distributed among the exposed groups it has no influence on the relative risk of lung cancer as a result of exposure to ETS found in cohort studies. In case-control studies misclassification of the effect variable causes the relative risk to be underrated.

Most studies, furthermore, did not distinguish between different types of lung tumour. Smokers have a more highly increased risk of squamous-cell and small-cell carcinomas than of adenocarcinomas (Wyn77). A small number of studies indicated that the risk of non-adenocarcinomas in the lung was also increased by exposure to ETS (Koo85, Wua85, Dal86, Per86, Gao87).. Lam et al., on the other hand, found a statistically significant increase only in the risk of adenocarcinomas, not of non-adenocarcinomas (Lam87a).

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4.3.3 Distortion of results due to information bias

In case-control studies knowledge of the "outcome" of exposure to ETS can influence the way it is reported. It is not clear whether patients with lung cancer or their housemates report smoking habits accurately or exaggerate or minimize them. The distortion could thus cause the effect to be either underrated or overrated (NRC86, USS86, Sar89).

As indicated in Chapter 2, incorrect reporting by respondents of their own smoking is a major distorting factor. As a result some respondents were found to have been incorrectly classified as non-smokers in the studies (Wal86a, Lee88, Pro88). It was also found that smokers (including ex-smokers and occasional smokers) were more likely than non-smokers to live with smokers (Gil84, Wal85, Lee88). It is

probable, therefore, that the majority of smokers/ex-smokers incorrectly classified as non-smokers fall into the exposed category (partners of smokers). Since the lung cancer risk in smokers/ex-smokers is much higher, this disproportionate misclassification could cause the effect of exposure to ETS to be overrated.

The extent of the overrating depends primarily on:

(a) the percentage of smokers, ex-smokers and occasional smokers incorrectly classified as non-smokers

(b) the magnitude of the additional lung cancer risk in this group

(c) the degree of preference smokers have for a partner who smokes

(d) the distribution of smokers in the population by sex.

Various researchers have analysed the influence of these factors on the relative risk of lung cancer found in the studies (NRC86, Wal86a, Lee88, Lee89). Wald et al. found that disproportionate misclassification of smoking habits had a marginal influence: the relative risk should have been 1.30 instead of the 1.35 found. In the opinion of the authors of the NRC report the relative risk of lung cancer of 1.34 found by them should have been 1.15-1.25, allowing for misclassification. Lee's analysis indicates that the effect found in the studies could be almost entirely due to misclassification (Lee89). The differences between the results of these analyses were due primarily to differing estimates of the percentage of smokers, ex-smokers and occasional smokers presenting themselves as non-smokers. This percentage was estimated on the basis of data on the relationship between reporting of smoking and results of biological monitoring. Lee's estimates were much higher than the other authors'. The Committee would point out that in all cases the data on the percentage of smokers incorrectly taken to be non-smokers were taken mainly from British research, whereas the epidemiological studies came from all over the world, including Japan and China.

There is no information available on differences between individuals in the sample as regards the correctness of the reporting of their own smoking. It may be that partners of smokers are more inclined to report their previous smoking than partners of non-smokers: this would result in more smokers being incorrectly classified as non-smokers in the reference group (partners of non-smokers) and thus cause the relative risk of lung cancer as a result of exposure to ETS to be underrated.

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4.3.4 <u>Confounders</u>

The earliest studies in particular failed to take sufficient account of other factors which could influence the occurrence of lung cancer. More recent studies correct for confounders such as socio-economic group, occupation and diet. It is not clear whether this is enough to rule out any possibility of distortion.

The influence of confounders increases the more these variables are related to smoking in households. A number of studies show that the presence of housemates who smoke goes

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together with an unhealthy lifestyle, measured in terms of e.g. quality of diet, overweight, alcohol consumption, high occupational risk, or unmarried status (Koo88a, Fri83, Sve87). The Committee would not rule out the possibility that the increased relative lung cancer risk found in non-smoking housemates of smokers could be partly due to these confounders.

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4.3.5 Selective publication

Vandenbroucke found no indications of distortion due to selective publication in the results of studies of non-smoking women, but was unable to exclude the possibility of publication bias in the results of studies of non-smoking men (Van88). Most of the papers related to non-smoking women (4.1). To ascertain whether there was actual publication bias, Wells traced unpublished findings of a number of studies of men: he concluded that they did not conflict with the published findings (Wel88).

On this basis the Committee considers it improbable that publication bias has caused the risks described to be seriously overrated.

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4.4 Biological plausibility

In the Committee's opinion an increase in the risk of lung cancer as a result of exposure to ETS accords with our current biological understanding of the influence of chemicals on the development of cancer. It bases this opinion on the following arguments.

(a) ETS contains a large number of substances capable of causing tumours in laboratory animals. It is known that some components of ETS can also be responsible for cancer in humans (IAR86).

(b) Components specific to ETS, e.g. nicotine and cotinine, have been found in the bodies of non-smokers.

(c) According to our present understanding, there is in theory no exposure threshold below which carcinogens capable of changing the genetic material in cells do not present an increasing cancer risk as exposure increases (Gez88).

On the basis of the results of biological monitoring it would not be reasonable, in the Committee's opinion, to conclude from the increased risk of lung cancer found in smokers that non-smokers exposed to ETS also have an increased risk. The composition of ETS and MS differs in both quality and quantity. There are differences between dust particles in ETS and MS which result in a different pattern of deposition in, and removal from, the lungs. Furthermore, differences have been found between smokers and non-smokers in the metabolism of components of tobacco smoke.

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4.5 Significance of the results of epidemiological research

A large number of studies in various countries throughout the world have found some increase in the risk of lung cancer on long-term exposure to ETS. A connection was

generally found, moreover, between the degree or duration of exposure and the magnitude of the increase. The findings were statistically significant in only a few studies. Combining the findings of different studies did produce results that were statistically significant and showed that the risk of lung cancer in non-smokers was increased by a factor of 1.1 to 1.6 by the presence of a partner who smoked. The Committee would point out, however, that there are considerable problems with combining data from studies of different types and designs, and the influence of the distorting factors mentioned remains unabated.

The Committee is of the opinion that the estimates of relative lung cancer risk in non-smoking partners of smokers published to date could be strongly influenced by the distorting factors mentioned.

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4.6 Conclusions

The Committee concludes that it is probable that long-term exposure to ETS could increase the risk of lung cancer. This view is based primarily on the findings of epidemiological research. It is also biologically plausible that ETS could have such an effect. The Committee's conclusion is in line with that of the National Research Council (NRC86) and the Surgeon General (USS86) in the US and with that of a recent detailed study of the literature (Spi90).

It is not possible to ascertain the influence of various distorting factors on the findings of the various studies. The Committee therefore finds itself unable to give a well-considered estimate of the increase in the lung cancer risk as a result of exposure to ETS. To do this further research is needed, and this should be designed in such a way as to make better allowance for the distorting factors mentioned than hitherto.

5 OTHER TYPES OF CANCER

5.1 Results of epidemiological research

Various epidemiological studies have examined the link between exposure to ETS and the occurrence of cancers other than lung cancer.

An extensive Japanese cohort study by Hirayama showed that spouses of smokers had a higher risk of brain tumours and tumours of the nasal cavity than those of non-smokers. The increase in the risk depended on the dose, expressed as the number of cigarettes a day smoked by the partner (Hir84). A case-control study by Brinton et al. also showed an increased risk of squamous-cell tumours of the nasal cavity on exposure to ETS (Bri84). Preston-Martin et al. in their case-control study found no link between the occurrence of brain tumours in children and maternal smoking, although they did find a connection with paternal smoking (Pre82).

In a case-control study among adults Sandler et al. found a statistically significant link between ETS dose from childhood onwards and the occurrence of breast cancer, cervical cancer and cancer of the endocrine glands in later life. The relative risks were 1.8, 1.8 and 3.2 respectively (San85b,c). In another case-control study Slattery et al. found statistically significant indications that exposure to ETS is a risk factor for cervical cancer (relative risk: 2.96; 95%CI: 1.25-7.03) (Sla89).

A case-control study by Burch et al. showed a doubling of the risk of bladder cancer in smokers. There were no indications that exposure to ETS was also a risk factor for this form of cancer (Bur89).

A retrospective study of a cohort of some 28,000 smokers and 19,000 non-smokers, with a follow-up period of 12 years, gave no indications that non-smokers who lived with smokers had an increased risk of cancer (San89).

A ten-year prospective study of a cohort of some 90,000 children showed almost a doubling of the risk of leukaemia in children as a result of maternal smoking during pregnancy (Neu71); the increase was not statistically significant. A case-control study by Stjernfeldt et al. showed an increase in the risk of leukaemia and lymphomata in children whose mothers smoked before, during and after pregnancy. The researchers found relative risks of 1.0, 1.3 and 2.1 where mothers smoked 0, 1-9 and more than 9 cigarettes a day respectively. The link was strongest with smoking before pregnancy and weakest with smoking after the birth (Stj86). Sandler et al. found an increased risk of leukaemia and lymphomata in children where one or both parents smoked (relative risk: 1.7 and 4.6

respectively) (San85c). Two studies, however, showed no link between parental smoking and the occurrence of leukaemia in children (Ste85, Man57). Gold et al. in a survey of a small group of children found a statistically insignificant link between the occurrence of brain tumours and maternal smoking before and during pregnancy (Gol79).

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5.2 Significance of the results

In the case of a number of cancers linked in the above studies with exposure to ETS (brain tumours, breast cancer and cancer of the endocrine glands) no link was found with active smoking. There could therefore be some doubt as to the validity of the first-mentioned findings, since smokers are exposed to ETS just as much as non-smokers, and they inhale the tobacco smoke directly. Slattery et al. found that exposure to ETS caused an increase in the risk of cervical cancer equal to that in smokers (Sla89). This finding is also difficult to interpret in view of differences in exposure to tobacco smoke.

The results of the research into the part played by ETS in the occurrence of cancer in adults (Hir84, San85a,b,c, San89) are difficult to assess; insufficient allowance - if any - was made for confounders.

There are no indications that cancer of the haematopoietic organs is linked with smoking. The possibility cannot be ruled out, however, that exposure of children or unborn children to ETS could have an effect that is not found in adults who smoke.

The indications that parental smoking has an influence on the occurrence of cancer of children's haematopoietic organs are not consistent. The definitions of exposure to ETS differed considerably. Parents who smoked during pregnancy usually also smoked before and after, consequently it is impossible to distinguish between teratogenic and post-natal effects (USS86).

As in the case of the epidemiological research into lung cancer, inaccuracies in determining doses or any disproportionate distribution of misclassification of smoking habits among the exposed categories may have resulted in distortion of the findings (see Chapter 4).

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5.3 Conclusions

The Committee is of the opinion that the results published to date are insufficiently reliable to permit an assessment to be made of the influence of exposure to ETS on the occurrence of cancers other than lung cancer. The reports of the Surgeon General and the National Research Council also come to this conclusion (USS86, NRC86).

It is known that some mutagenic and carcinogenic components of tobacco smoke can pass through the placenta and thus reach developing tissues (Per89, Eve86). To what extent such exposure of the unborn child increases the risk of cancer in later life is not known: no relevant data are available from epidemiological research.

6 CARDIOVASCULAR DISEASE

6.1 Introduction

A large number of studies have shown that degenerative vascular diseases such as coronary artery disease, certain types of brain haemorrhage and thrombosis are more common in smokers than in non-smokers (USS83, NRC86, Shi89). In this Chapter the Committee summarizes the data on the influence of exposure to ETS on the occurrence of cardiovascular disorders

It is assumed that any effect on the cardiovascular system is caused primarily by the nicotine and carbon monoxide (CO) in tobacco smoke (NRC86, USS86, Sch84). Nicotine influences heartbeat and blood pressure. Because haemoglobin has a much greater affinity for CO than for oxygen, exposure to CO results in an increase in the quantity of carboxyhaemoglobin (COHb) in the blood, which reduces the capacity of the lungs and tissues to absorb oxygen. Bonding of CO to myoglobin can result in an oxygen deficiency in muscle tissue. Various studies have shown that exposure to tobacco smoke or components contained in it affects blood clotting and arterial walls and the composition of lipids and lipoprotein fractions in the blood (Ast79, Dav89, Sch84, Cra89, Gla90).

6.2 Acute effects

Exposure to tobacco smoke increases the fraction of haemoglobin bonded to carbon monoxide (COHb) in the blood. In smokers the fraction varies from 4 to a maximum of 12 percent. In non-smokers exposed to ETS it rises to no more than 1.5 or 2 percent. Normally it varies between 0.5 and 1 percent (Sch84, WHO87, EPA84). Because of the large amount of oxygen needed by the heart, effects of carbon monoxide manifest themselves first in people exercising and people with heart disorders (EPA84, WHO87).

When healthy volunteers were exposed to ETS no significant effects were found on heartbeat, blood pressure or recovery after exercise (Pim78, She79b, NRC86). McMurray et al. found that exposure to ETS had a slight effect on heartbeat and oxygen intake in young healthy women exercising (McM85).

Angina pectoris is the term used to denote symptoms resulting from an inadequate supply of oxygen to the cardiac muscle, which is usually caused by narrowing of the coronary arteries: these are exemplified by radiating pain and pressure in the chest. Significant increases in heartbeat and blood pressure were found in patients exposed to CO or ETS during exercise, and an increase in disorders at COHb levels of three

1.1-1.6) for male and 1.2 (95% CI: 1.1-1.4) for female non-smoking partners of smokers. He also found that the relative risk of IHD was greatest in 50-year-olds, declining after that age (Wel88).

In a retrospective cohort study of some 28,000 smokers and 19,000 non-smokers Sandler et al. found no increase in the relative risk of death from brain haemorrhage in males with partners who smoked (0.97; 95% CI: 0.65-1.46) but did find an increase in the case of women (1.24; 95% CI: 1.03-1.49). They made no correction for known risk factors (San89).

Lee et al. in a small case-control study also found a slight increase in the risk of cerebrovascular disorders in non-smokers with partners who smoked. The result was not statistically significant (Lee86).

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Table 6 Results of the principal epidemiological studies of ischemic heart disease in non-smoking partners of smokers

Source	Number	Sex	RR*	95% CI	Country	DRR** (Yes/No)	Corrected for
Prospective cohort [cijfers overnemen - komma wordt punt]							
Hirayama 1984		F			Japan	Y	Age
Garland 1985		F			USA	N	Age, blood pressure, cholesterol, weight, length of marriage
Svendsen 1987		M			USA	Y	Age, blood pressure, cholesterol, weight, education, drinking
Helsing 1988		F M			USA	Y	Age, dwelling, marital status, education
Hole 1989		M+F			UK	-	Age, sex, social class, blood pressure, cholesterol, weight
Humble 1990		F			USA	Y	Age, cholesterol, blood pressure, weight
Case-control							
Lee 1986		F M			UK	-	Age, marital status
Martin 1986		F			USA	-	Age, IHD in family, hypertension, diabetes, weight, drinking, training
Henderson 1989		F			China	Y	Age, race, place of residence, occupation, hypertension, hypertension & IHD in family, hyperlipidemy

* Relative risk
** Dose-response relationship found

Tabel 6 Resultaten van de belangrijkste epidemiologische onderzoeken naar ischemische hartziekte bij niet-rokende partners van rokers.

bron	aantal	sexe	RR*	95%-BI	land	BRR** (Ja/Nee)	gecorrigeerd voor
prospectief cohort							
Hirayama 1984	494	V	1,2	0,9- 1,4	Japan	J	leeftijd
Garland 1985	19	V	2,7	0,9-13,6	USA	N	leeftijd, bloeddruk, cholesterol, gewicht, duur huwelijk
Svendsen 1987	13	M	2,1	0,7- 6,5	USA	J	leeftijd, bloeddruk, cholesterol, gewicht, opleiding, alcohol
Helsing 1988	988 370	V M	1,2 1,3	1,1- 1,4 1,1- 1,6	USA	J N	leeftijd, woning, huwelijkse staat, opleiding
Hole 1989	84	M+V	2,0	1,2- 3,4	UK	-	leeftijd, geslacht, sociale klasse, bloeddruk, cholesterol, gewicht
Humble 1990	76	V	1,6	1,0- 2,6	USA	J	leeftijd, cholesterol, bloeddruk, gewicht
patiënt-controle							
Lee 1986	77 41	V M	0,9 1,2	0,7- 1,3 0,5- 2,6	UK	-	leeftijd, huwelijkse staat
Martin 1986	23	V	2,6	1,2- 5,7	USA	-	leeftijd, IHZ in familie, hypertensie, diabetes, gewicht, alcohol, training
Henderson 1989	34	V	3,0	1,3- 7,2	China	J	leeftijd, ras, woonplaats, beroep, hypertensie, hypertensie en IHZ in familie, hyperlipidemie

* relatief risico

** blootstellingsresponsrelatie waargenomen

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6.3.4 Significance of the results of epidemiological research

In virtually all the studies the exposure was determined from the partner's smoking habits. The innaccuracy of the exposure variables may have caused the effect of exposure to be underrated.

As in the lung cancer studies, awareness of the outcome may have influenced the reporting of exposure to ETS in the case-control studies.

Smoking causes a substantial increase in the relative risk of IHD. More smokers may have been incorrectly included in the exposed category than in the non-exposed category in the research into IHD (see 2.3.5), which may have caused the risk to have been overrated to some extent. As in the case of the lung cancer studies, it is not likely, in the Committee's opinion, that the increase found in the risk is entirely due to disproportionate misclassification of smoking habits.

Allowance has to be made for the possibility that the increased risk of IHD found could be due to differences in lifestyles and habits between non-smokers with and without housemates who smoke. The study by Garland et al. found no differences between the two categories in potential confounders such as blood pressure, serum cholesterol levels and obesity (Gar85b). Svendsen et al. also found no differences in blood pressure, serum cholesterol levels and certain psychosocial factors, but they did find that men married to smokers weighed more and drank more (Sve87). In a study in Hong Kong Koo et al. established on the basis of a large number of variables that non-smoking spouses of non-smokers generally lived more healthy lives than non-smoking spouses of smokers as regards such things as diet, drinking, use of prescribed and proprietary medicines and parental smoking habits (Kooa,b,c,d,e). In a study of some 38,000 non-smokers and ex-smokers Friedman et al. demonstrated a link between (a) exposure to ETS and (b) alcohol/marijuana use and dangerous occupations (Fri83).

The Committee would therefore not rule out the possibility that the increased relative risk of IHD found in the research could be due to confounders linked with housemates' smoking habits.

The Committee would point out that a slight increase in the relative risk of IHD would result in far more cases of disease and mortality than, for example, a slight increase in the relative risk of lung cancer. In the Western world IHD is also common in non-smokers, whereas lung cancer is uncommon (see e.g. Wel88).

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6.4 Conclusions

The Committee would not expect short-term exposure to ETS in healthy people to have an adverse effect on the circulation in normal circumstances. It would not rule out the possibility that short-term intense exposure to ETS in very smoky rooms could cause or aggravate disorders in angina pectoris patients. The levels here are such, however, that

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other irritating effects of ETS would already have made the air in the room unpleasant (see Chapter 9).

Nor would the Committee rule out the possibility that long-term exposure to ETS could increase the risk of cardiovascular disease. There are weak indications of this from epidemiological research among non-smoking partners of smokers, and an effect of this kind is also found in smokers. Furthermore, both smoking and exposure to individual components of tobacco smoke affect arterial walls, blood lipid composition and blood clotting.

On the other hand, the link found between exposure to ETS and the occurrence of ischemic heart disease could to a large extent be due to differences in lifestyles and habits between non-smokers with and without partners who smoke. In line with the reports of the NCR (1986) and the US SG (1986) the Committee is of the opinion that further research is needed to establish the extent to which this is a causal connection, and this research should make more allowance than hitherto for the influence of the distorting factors mentioned, in particular the confounders.

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7 EFFECTS ON CHILDREN

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7.1 Introduction

The research into the effects of exposure to ETS on the health of children has concentrated primarily on the respiratory tract, although the part played by ETS in the development of middle ear infections has also been investigated. In this Chapter the Committee summarizes the data on the effects of ETS on children and briefly considers the possible effects of indirect exposure on unborn children whose mothers smoke, or are exposed to ETS, during pregnancy.

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7.2 Methodological problems

There are a number of particular methodological problems affecting epidemiological research into the effects of exposure to ETS on the respiratory tract in children.

In children of about ten and upwards their own smoking could cause distortion of the results. Since children of parents who smoke begin smoking at an earlier age than children of non-smoking parents, the effects of exposure to ETS could be overrated when comparing these two categories.

Parents with respiratory tract disorders are more inclined to report those of their children than parents without such complaints. Since parents who smoke are more likely to suffer from respiratory symptoms, these could also cause the effects of ETS to be overrated when comparing children of parents who smoke with those of non-smoking parents.

Smokers may be more susceptible to respiratory infections than non-smokers (Aro82, Kar82). Children of parents who smoke would thus be more likely to come into contact with people with respiratory infections, which could partly explain the greater frequency of these infections.

It is difficult to ascertain whether effects on the health of children are the result of exposure in the uterus or also of post-natal exposure to ETS. Moessinger concludes from an analysis of epidemiological research and experiments on animals that smoking during pregnancy affects the development of the lungs in the foetus (Moe89).

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7.3 Results of epidemiological research

In this section the Committee summarizes the results of epidemiological research; for a detailed description of the various studies the reader is referred to the literature (NRC86, USS86, Sam83, Sam87). Various effect variables have been used in research into the effects of ETS on the

respiratory tract, both subjective, e.g. reporting of respiratory complaints and infections, and objective, e.g. measurements of pulmonary function. The latter calls for a certain amount of explanation.

After birth ETS enters the body through the respiratory tract and lungs and is thus able to influence lung development in the growing child and the ventilatory function of the lungs. The development of the lungs is able to be influenced because the development of alveoli continues until about seven years after birth. The alveoli determine the area available for gas exchange and the volume of the lungs. The ventilatory function can be affected if the capacity of the airways is reduced, which can be caused by inflammation, increased secretion and the like. Reduced capacity is generally detected from measurements of the volume of air that can be expelled by forced expiration in one second (FEV1), or the maximum volume flow that can be achieved half-way through a forced expiration (referred to as MMEF or MEF50, depending on the method of measurement used). These and other similar indices of capacity are often referred to as "pulmonary function".

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7.3.1 Respiratory infections and disorders

A large number of studies, many of them extensive, have investigated whether parental smoking is linked to the occurrence of respiratory infections and disorders. The effect variables used were data on hospitalization for pneumonia and bronchitis, tonsillectomies and adenoidectomies, general practitioners' diagnoses of bronchitis and tracheitis, and parents' reports of respiratory disorders such as chronic cough, expectoration, wheezing and short-windedness (Cam69, Col71, Har74, Leb76, Lee76a,b, Sch77, Sai78, Sim78, Ran78, Bla78, Wei80, Fer81, Pul82, Dod82, Ekw83, Sch83, Hal84, War84, Cha84, Fer85a, Ped85, Bur86, Yue86, McC86, McC89, Tay87, Ste87, Doc87, Wie87, Che86, Che88, Che89, Som88, Neu89, Dij90).

The results of these variously designed studies in different countries indicate that parental smoking increases the risk of respiratory infections and complaints in children. There are strong indications that the risk of hospitalization for respiratory infections in the early years increases by 50 to 100 percent if the parents, especially the mother, smoke (Har78, Ran78, Ekw83, Hal84, Che88, Tay87). The link between parental smoking and the occurrence of respiratory infections is particularly strong in children under the age of two. This may be connected with the continuous immediate proximity of the mother at this stage and the fact that the immune system is not yet fully developed (USS86).

Research into respiratory complaints reported by parents showed that children with parents who smoked had a greater risk (by a factor of 1.1 to 2) of symptoms than children with non-smoking parents. In some cases an even greater increase was found, up to a factor of 6 or more.

It was found in various studies that the risk of respiratory infections and complaints increased as the number of cigarettes smoked in the home went up (Har74, Col74, Bla78, Wei80, Dod82, War84, Cha84, Doc87, Som88, Neu89, Dij90).